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Original Article

Evaluation of Changes in Macular Thickness following Nepafenac Ophthalmic Drops in Chronic Diabetes

Muhammad Jahanzaib, Fakhar Humayun, Saad Naseer, Usman Tariq, Fawad Ahmad Khan, Waqas Rahim Butt

Department of Ophthalmology, Armed Forces Institute of Ophthalmology/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

Objective: To compare the efficacy of Nepafenac ophthalmic drops in reducing macular inflammation and thickness in chronic diabetic retinopathy using optical coherence tomography (OCT).

Study Design: Quasi-experimental study.

Place and Duration of Study: Department of Ophthalmology, Armed Forces Institute of Ophthalmology, Rawalpindi Pakistan, from Jan to Dec 2023.

Methodology: Before initiating treatment, visual acuity was assessed using a standard Snellen chart and documented in the patient records. Baseline foveal thickness was measured in all participants using optical coherence tomography (OCT). All patients then started on 0.1% Nepafenac ophthalmic drops, administered as one drop in each eye twice daily for six months. The primary outcome measures were the change in visual acuity and the change in mean foveal thickness, both evaluated after six months using OCT.

Results: Change in visual acuity (converted from Snellen values to LogMAR) was 0.79±0.21 log units before starting medical treatment, and it was 0.62±0.16 after six months of medical therapy (p<0.001). Change in foveal thickness as assessed by OCT (optic coherence tomography) was 472.14±76.02 microns before the start of medical therapy, and it was 253.69±47.26 microns after six months of treatment (p<0.001).

Conclusion: The study concludes that Nepafenac ophthalmic drops effectively improve macular edema, reduce foveal thickness, and enhance visual acuity in patients with diabetic retinopathy who present with a pre-treatment visual acuity of less than 6/12 on the Snellen Chart.

Keywords: Diabetes, Macular, Nepafenac, Optic Coherence Tomography, Ophthalmic, Retinopathy.

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INTRODUCTION

Diabetes is one of the most prevalent endocrinological diseases worldwide.[1] According to recent estimates published by The Lancet Global Health in 2023, around half a billion people are living with the disease, constituting all genders and age groups, with the number projected to increase to 1.3 billion in the next 30 years.[2] Pakistan currently ranks among the top 5 countries in South Asia with the highest number of cases living with diabetes.[3] The current estimated population living with the disease is around 26.7% making the total cases approximately 330 million.[4]

Diabetes is a complex endocrinological disease affecting all systems of the body. Impaired insulin secretion and/or increased resistance are the primary disorders resulting in a diverse picture of clinical signs and symptoms.[5] The major organ systems most affected are the vascular, renal, and ophthalmic.[6] Diabetic retinopathy is the most common and severe microvascular complication. If not detected early and treated properly, it has major deteriorative effects on the retina, ultimately leading to blindness.[7] Diabetic macular edema (DME) follows the course of the disease, resulting in retinal thickening by accumulation of intraretinal fluid in the inner and outer plexiform layers of the eye.[8]

The treatments available for the complication include focal laser treatment as well as intravitreal injections. Neither is without its drawbacks. Focal laser treatment has been shown to lessen vision loss and improve vision gain, but the reduction in macular edema is often less than satisfactory, as evidenced by the literature.[9] The drawback of a permanent scotoma is also associated when targeting microvascular aneurysms at the foveal avascular zone, which is avoided in a focal laser. A laser FAZ is an inadvertent effect of the laser. Intravitreal injection carries the risk of bleeding and endophthalmitis.[10] Invasive treatments are usually not warranted in mild to

Correspondence: Dr Muhammad Jahanzaib, Department of Ophthalmology, AFIO, Rawalpindi Pakistan

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moderate macular edema, according to the Treatment and Surveillance (T and S) protocol of the Diabetic Retinopathy Clinical Research Network (DRCR.net), with anti–vascular endothelial growth factor (anti-VEGF) therapy reserved for severe cases presenting with a pre-treatment visual acuity better than 6/12. In such cases, non-invasive medical therapy may be advantageous, avoiding the potential complications associated with invasive procedures. Nepafenac belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs). Given that inflammatory mediators are elevated and play a significant role in the pathophysiology of macular edema, nepafenac offers a potential therapeutic approach targeting this inflammatory component without risk of interventions.

In our setting, evaluating the efficacy of nepafenac as a standalone treatment is of particular interest, as it may provide an easy-to-administer, well-tolerated, and cost-effective alternative for patients. This approach may be especially beneficial for individuals who do not require invasive therapy and can achieve favorable outcomes with medical management alone, thereby avoiding the risks and higher costs associated with surgical or injectable interventions. Keeping in view these benefits, the study was conducted on patients with retinopathy secondary to chronic diabetes.

METHODOLOGY

This quasi-experimental study was carried out at the Department of Ophthalmology, Armed Forces Institute of Ophthalmology, Rawalpindi Pakistan, from Jan to Dec 2023 after approval from the ethical review board vide letter no.312/ERC/AFIO. The sample size was calculated keeping the mean change in foveal thickness before and after Nepafenac treatment being 417 microns versus 267 microns, respectively.[11] Minimum sample size came out to be 70 patients according to the WHO calculator with the population variance at 1,00,000. The study included 350 patients to establish the study outcomes.

Inclusion Criteria: Patients of both genders aged over 50 years, diagnosed with diabetes mellitus according to World Health Organization (WHO) criteria, were eligible for inclusion. Participants were required to have clinical and imaging findings consistent with diabetic retinopathy and macular edema, confirmed by optical coherence tomography (OCT), along with a threshold visual acuity of less than 6/12 on the Snellen chart.

Exclusion Criteria: Patients of both genders under 40 years, with complete or near complete blindness due to the disease, patients with focal laser surgery or intravitreal injections for treatment of macular edema and vision improvement, patients with advanced cardiac or respiratory disease, patients with severe end-organ damage, and patients unwilling to be included in the study.

All patients meeting the inclusion criteria were enrolled in the study. Before induction, participants were thoroughly counselled regarding the study protocol. All agreed to maintain regular monthly follow-up visits in the outpatient department (OPD) or, when necessary, via telephone to confirm compliance with the prescribed treatment regimen. Patients who failed to attend follow-up visits or did not adhere to the treatment protocol were excluded before the final assessment (Figure).

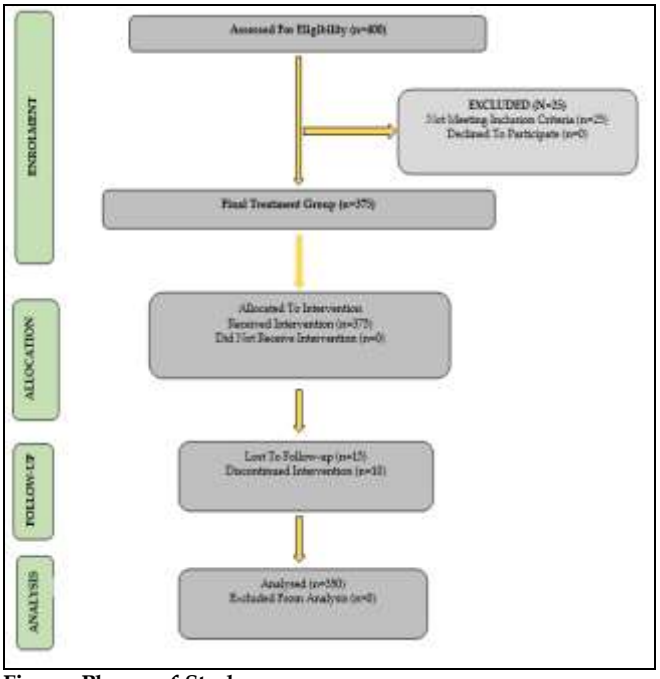

Figure: Phases of Study

Before initiation of treatment, visual acuity was confirmed by using a standard Snellen chart and documented in the patient's details. Pre-treatment subfield macular thickness was noted by OCT in every patient included in the study. Treatment was started in all patients with 0.1% Nepafenac ophthalmic drops, one drop in each eye twice a day for 6 months. At the end of six months, visual acuity was checked again using Snellen charts, and values were converted into LogMAR using SPSS to streamline the results. Mean

subfield macular thickness was also measured in all patients at the end of 6 months by OCT and was compared. Patients who did not follow-up or gave a history of non-compliance with treatment were excluded from the study. Primary variables studied were the change in visual acuity after six months and the change in mean foveal thickness as checked by OCT after six months.

Data was analyzed by using Statistical Package for Social Sciences (SPSS) 22.00. Quantitative data was represented using mean ± standard deviation and qualitative data was represented by using percentage and frequency. A paired samples t-test was used to compare statistically significant means before and after treatment in the study group. A *p*-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 375 patients were initially added to the study, but 15 patients failed to follow-up, and 10 patients were not compliant with the medication. A total of 350 patients were included in the final protocol for analysis. The mean age of patients in the study group was 47.83±9.31 years, and the mean weight of patients in the study group was 68.48±3.04 kg. Gender distribution revealed 139(39.7%) patients were male and 211(60.3%) were female. The mean duration of diabetes in the study group was 16.17±2.52 years. During the duration of treatment, NSAID (non-steroidal anti-inflammatory drugs) induced keratosis was seen in 07(2.0%) of patients in the study group (Table-I).

Table-I: Demographic and Clinical Characteristics (n=350)

Characteristics	Treatment Group (n=350)
Mean Age (Years)	47.83±9.31
Mean Weight (Kg)	68.48±3.04
Gender	
Male	139(39.7%)
Female	211(60.3%)
Mean Duration Of Diabetes Diagnosis (Years)	16.17±2.52

When studying the primary variables before and after six months of treatment, change in visual acuity (converted from Snellen values to LogMAR) was 0.79±0.21 log units before starting medical treatment, and it was 0.62±0.16 after six months of medical therapy (p<0.001). Change in foveal thickness as assessed by OCT was 472.14±76.02 µm before the start of medical therapy, and it was 253.69±47.26µm after six months of treatment (p<0.001). Mean HbA1C levels were 6.70±0.76% before the start of therapy, and they were 6.68±0.78% after treatment for six months (p=0.759) (Table-II).

Table-II: Clinical Variables Compared Before and After Treatment (n=350)

Variable	Before Treatment (n=350)	After Treatment (n=350)	*p*-value
Change In Visual Acuity (LogMAR Units)	0.79±0.21	0.62±0.16	<0.001
Change In Foveal Thickness (µm)	472.14±76.02	253.69±47.26	<0.001
HbA1c Level (%)	6.70±0.76	6.68±0.78	0.759

**LogMAR - Logarithm of the Minimum Angle of Resolution*
HbA1c - Glycosylated Hemoglobin

DISCUSSSION

The findings of the study conclude that Nepafenac ophthalmic drops improve macular edema, foveal thickness, and visual acuity in patients with diabetic retinopathy with a pre-treatment visual acuity of <6/12 on the Snellen chart. It is a suitable, non-invasive, convenient, compliant, and cost-effective alternative to invasive procedures for the treatment of macular edema in patients with chronic diabetes. The study aimed to standardize treatment modalities in our setting, which caters to a large patient load from across the country. A significant proportion of these patients originates from resource-limited and remote areas, where cost-effectiveness and maintaining regular follow-up present major challenges. Simple medical therapy and twice-yearly follow-up would greatly address these issues for the majority of this region.

Among the primary variables assessed, a statistically significant improvement in visual acuity was observed when comparing pre- and post-treatment measurements on the standard Snellen chart. The majority of patients maintained their baseline visual acuity, while a substantial proportion demonstrated notable improvement. Importantly, no patient in the study experienced a decline in visual acuity by the end of the treatment period, underscoring the potential benefit and safety of the administered therapy.

The world has improvised treatment regimens through a variety of alternatives. The use of Anti-VEGF treatment in patients with macular pathology in diabetes is now being offered in mainstream setups worldwide,[12] but its cost-effectiveness and limited availability to major centers in our country warrant

alternate methods for patients who do not have access to this treatment option. Since local studies for the subject were scarce, this study hopes to produce findings that would allow physicians to opt for medical therapy in patients with mild to moderate macular disease caused by diabetic retinopathy.

The mean age of patients in our study group was in the early fifties. This is in line with the mean age of diagnosis in various demographic areas according to Li *et al*.[13] In Africa, America, and Europe, the mean age falls between mid to late forties to early fifties. Our study showed that there was a female predominance, which is also supported by Teo *et al*., showing that females are affected more than men.[14] It is supported by the study of Brar *et al*., highlighting that females with type-II diabetes are more prone to develop diabetic retinopathy. Studies in rural areas show that limited access to appropriate healthcare services results in more ophthalmic complications in females than in males.[15] This is especially true for areas in Southeast Asia and Africa, as claimed by Wykoff *et al*.[16]

The mean duration of diabetes in patients was around 15 years when diagnosed with diabetic retinopathy. This is more than the mean age in other developed countries shown by the study of Thagaard *et al*.[17] Poor compliance, difficult access to healthcare services are proposed as the possible reason why the diagnosis is made much later in the course of the disease in patients presenting to our demographic setup. Notable improvements in visual acuity of this study have also been shown in the study conducted by Ahmad *et al*.[18] When treatment with NSAIDs was done for macular disease in diabetic retinopathy patients, the foveal thickness on OCT before and after therapy was significantly improved with medical treatment for six months. This is evidenced and supported by literature as well, with studies done by Singh *et al*.[19]

LIMITATION OF STUDY

This study was conducted at a single tertiary care center with a relatively small sample size, which may limit the generalizability of the findings. The quasi-experimental design lacked randomization and masking, introducing the possibility of selection and observer bias. Follow-up was limited to six months, restricting the evaluation of long-term efficacy and recurrence rates. Objective imaging analysis was confined to OCT measurements without patient-reported outcome assessments.

CONCLUSION

We conclude that Nepafenac ophthalmic drops improve macular edema, foveal thickness, and visual acuity in patients with diabetic retinopathy with a pre-treatment visual acuity of <6/12 on the Snellen chart.

Conflict of Interest: None.

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

MJ & FH: Data acquisition, data analysis, critical review, approval of the final version to be published.

SN & UT: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

FAK & WRB: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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